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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,091	05/06/2005	Juha-Matti Savola	TUR-168	2654

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
08/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,091	SAVOLA ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23 and 25-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 25-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The respond filed on 6/23/10 has been entered.

2. Applicant's arguments filed 6/23/10 have been fully considered but they are not deemed to be persuasive.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 23 and 25-33 are pending in this office action.

5. Claims 23, 25-29 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huupponen (1995) in view of Karjalainen et al., (US 5,498,623) for the reasons made of record in Paper No. 20100225 and as follows.

Applicant argues that (i) "the record also demonstrates that those of ordinary skill in the art believe the mechanism of QTc prolongation is based on electrochemical modification of the action potential, and not on a particular administration route of the drug and that Huupponen and Karjalainen fail to disclose or suggest whether fipamezole will prolong QTc.

Applicant further argues that the "patent office must consider fipamezole's QTc prolongation properties and that the patent office objection that the claims do not recite

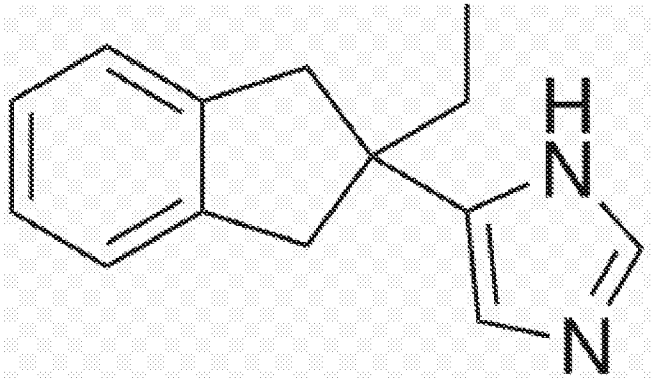
a QTc limitation ... is premature". It is furthered argued that Application Example 8 demonstrates fipamezole can prolong QTc when orally administered, but surprisingly does not prolong QTc when oromucosally administered at the same dosage amounts'.

(ii) that "QTc prolongation is independent from heart rate"

(iii) "the absence of QTc prolongation is unexpected and surprising

(iv) the claims properly omit dosage amount.

In response with regards to item (i) above, the claims are directed to a method of administering a formulation comprising an active ingredient of formula I, comprising oromucosal administration. Huupponen teaches administering atepamezole (i.e.,



) that has the same core, same class and functionally and structurally similar to the claimed compound fimpamezole wherein R1 and R2 are different substituents (i.e., hydrogen's in Huupponen versus halogen or hydroxy in the claimed invention). As previously made of record in Paper No. 20100225 "products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, and specifically teach the same administration mode the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990), "Where the

claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established".

The argument that the art believe the mechanism of QTc prolongation is based on electrochemical modification of the action potential, and not on a particular administration route of the drug, and that Huupponen and Karjalainen fail to disclose or suggest whether fipamezole will prolong QTc is found not persuasive because Huupponen teaches that the above compound is administered oral mucosally (via spraying into the buccal cavity). Emphasis added the drug is administered via oral mucosally (oromucosally). Therefore the same property is expected (i.e., fipamezole will prolong QTc).

With regards to the argument (ii) that QTc prolongation is independent from heart rate is found not persuasive because a review of literature indicates that QTc prolongation was dose and concentration dependant. For example, or as evidenced by Funck-Brentano et al., rate dependence of the drug sotanol induced QT prolongation (see page 539), (rt. col. lines 6+). Since QTc is associated with heart rate and the rate of the heart is unchanged, it is therefore reasonable that there is no prolongation of QTc was evident (see entire document). Secondly, the claims fail to recite a particular dosage amount, which is relevant in calculating a QTc value. There should be a correlation of amount administered with the QTc value.

Applicant further argued (iii) "Oral administration of fipamezole causes dose-dependent QTc prolongation - the higher the plasma concentration, the longer the QT

interval is prolonged. Thus, in the dog, oral administration of fipamezole at 5 mg/kg/day dosage prolonged the QTc interval by 14.0 ms, while a 10 mg/kg/day dosage prolonged the QTc interval by 25.0 ms" and asserts that the absence of any QTc prolongation when fipamezole is oromucosally administered cannot be predicted from Huupponen. Again applicant is arguing what is not claimed. All that is required in the claims is to administer the formulation via oromucosally. Therefore once the formulation comprising fipamezole is administered via the same route the properties will remain the same whether or not Huupponen recites it or not.

Lastly with regards to (iv) that the office objection that the claims do not recite dosage amount is without merit is found not persuasive. There is no medication given without an effective dosage amount. From claim interpretation any amount of fipamezole can be administered. The argument is not commensurate in scope with the claims because Huupponen teaches administering atepamezole (i.e., see above structure) that has the same core, same class and functionally and structurally similar to the claimed compound fimpamezole. Atepamezole is a homolog of fipamezole and shares the same characteristics with fimpamezole. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious. In re Hass, 60 USPQ 544 (CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950). Also recognized classes of chemical compounds mean that there is an expectation in the art that members of the same class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other with the expectation that the same intended result would be achieved.

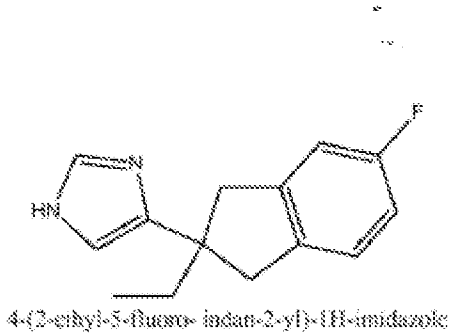
The teachings of Karjalainen encompass compounds of Huupponen, therefore one of ordinary skill in the art would be motivated to substitute Huupponen's compound with Karjalainen's compound and expect the same result. Applicant's argument that "one of ordinary skill in the art, aware that oral administration of fipamezole causes a dose-dependent prolongation of the QTc interval, would expect an equivalent or longer QTc prolongation if fipamezole was oromucosally administered" is found not persuasive because as clearly stated QTc is dose dependent. Moreover, the therapeutic activity that is relied upon by Applicant is a functional characteristic that is inherently or intrinsically present upon the administration of the drug in a certain dosage amount. The argument that the cited prior art fails to disclose or suggest that oromucosal administration of fipamezole will avoid QTc prolongation is found not persuasive because Huupponen specifically teach that in their study plasma, and heart rate were practically unchanged. Therefore if the plasma concentration is unchanged, there will be no "QTc prolongation", which further is not required within the claims.

Applicant's arguments have been fully considered but they are not persuasive as discussed above and already made of record.

In Summary:

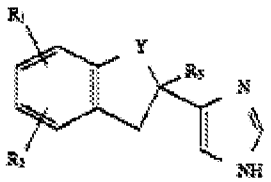
Huupponen teaches an α_2 adrenergic receptor antagonist (a species of the generic formula I in its acid salt) that is administered in the form of a spray oromucosally (see page 506, abstract; and Introduction as required by instant claim 23 in part, dissolved in ethanol and water (i.e., solvent; as required by instant claims 26- 27 in the form of spray as required by instant claims 31 and 32.

However Huupponen fails to teach the exact compound

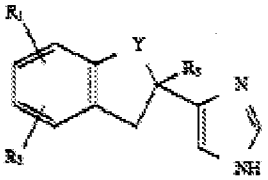


as required by instant claims 23 and 35 in part, and also fails to teach the formulation consists of a preservative (i.e., methyl parahydroxybenzoate) and the flavoring agent aspartame and black currant as in claims 29-30 and 33, and also the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29).

Karjalainen et al. teach the claimed compound as in current claim 23

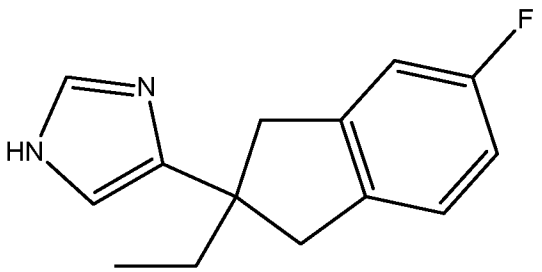


which is identical to the claimed compound of the claimed invention

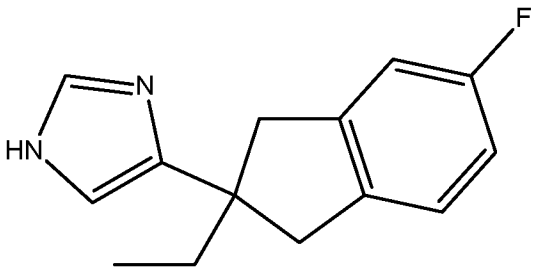


, wherein Y is CH_2 or CO, R_1 is a halogen or hydroxyl, R_2 is hydrogen or halogen and R_3 is hydrogen or lower alkyl-methyl (see abstract in a pharmaceutical composition administered orally (see abstract and also see col. 4, lines 62-63). Reasonably to have an oromucosal administration.

With regards to claim 25 Karjalainen teaches (see abstract



also) 4-(2-ethyl-5-fluoro-2,3-dihydro 1H indan-2-yl)-1H-imidazole is the same as



4-(2-ethyl-5-fluoro- indan-2-yl)-1H-imidazole or its acid salts (i.e., hydrochloride salt of (see col. 7, lines 48-50).

Karjalainen et al. also teach that the solvent is ethanol (as required by instant claim 27; see col. 7, lines 63-64).

However Karjalainen fails to teach specifically oromucosal administration and the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29, 31-33). Even though Karjalainen failed to teach the addition of flavoring and or preservative it is however taught that “choosing auxiliary ingredients for the formulation is routine to the ordinary skill in the art and is evident that suitable solvents, colors etc are used in a normal way”.

That being said it would have been obvious to one of ordinary skill in the art to add flavoring (i.e., sweetener) to the spray formulation for the improvement of the taste

since the patient would preferably and willingly administer the sweet tasting spray versus a bitter tasting spay that is directly placed in the oromucosal cavity.

It would have been obvious to add a preservative to any drug formulation for the prolongation of shelf life. These are routine procedures employed in the art of formulation as indicated above by Karjalainen. It would have been obvious to one of ordinary skill in the art would have substituted Huupponen's compound with Karjalainen's since both compounds are α_2 adrenergic receptor antagonists and one would have reasonably expected the formulation for oromucosal to be successful.

6. Claims 23, 25-30 and 31-33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Huupponen (1995) and Karjalainen et al., (US 5,498,623) in view of De Prost (US 6,413,988) for the reasons made of record in Paper No. 20100225 and as follows.

Applicant argues that the above rejection is traversed for the reasons previously discussed in remarks made on 12/30/09.

In response the argument was properly addressed in the response dated 2/25/10.

In summary:

Huupponen and Karjalainen are applied here as above. However both Huupponen and Karjalainen fail to teach the addition of a preservative and a flavoring agent to the formulation (as required by instant claims 26, 28, 29, 30 and 33).

De Prost teaches an aqueous pharmaceutical solution of prucalopride employed as a spray for oral administration that comprises a preservative for inhibiting the growth of micro-organism (see col. 2, lines 30-45 and col. 3, lines 14-16) wherein the preservative is a parahydroxybenzoate salt (see col. 4, lines 58-67) and the flavor is aspartame and black currant (see col. 2, lines 46-47 and col. 3, lines 1-4).

However De Prost fails to teach the claimed compound femiprazole and oromucosal administration.

It would have been obvious to one of ordinary skill in the art to have employed the teaching of De Prost of a spray formulation with a preservative and a sweetener with the teaching set forth by Huupponen and Karjalainen because as taught by De Prost these are added to liquid oral formulations such as sprays to inhibit microbial growth and to affect the taste by masking the bitter tasting effect. As known to one of ordinary skill in the art, aspartame is an intense sweetener and therefore capable of masking taste and black currant would give a fruity taste to the formulation and may enhance the sweetening capability of aspartame when combined.

Thus, the claimed invention was prima facie obvious to make and use at the time it was made.

Response to Affidavit

7. The declaration submitted by Juha-Matti Savola under 37 CFR 1.132 filed 6/23/10 is insufficient to overcome the rejection of claims 23, 25-30 and 31-33 based upon the rejection set forth by Huupponen (1995) and Karjalainen et al. (US 5,498,623)

or Huupponen (1995) and Karjalainen et al. in view of De Prost (US 6,413,988) as set forth in the last Office action:

Declarant argues that (i) QTc prolongation is independent from heart rate, and can occur even though heart rate remains unchanged. See paragraph 12 of Dr. Seiler's Declaration. (ii) that those of ordinary skill cannot predict whether oromucosal administration of fipamezole will or will not prolong QTc from Huuponen and those of ordinary skill will abandon a drug candidate which prolongs QTc and that (iii) the dog toxicity data can be extrapolated to clinical dosages and that .

In response the properties argued are inherent to the compound. Alternatively, a side by side comparison should be done with the prior art of record to prove that the same dosage of the same drug administered oromucosally would not have the same effect.

Secondly the declaration of Juha-Matti Savola and Jurg P. Seller under 37 C.F.R. 1.132 is an opinion declaration wherein the argument that the dog toxicity data can be extrapolated to clinical dosages maybe persuasive if the claims required/recited such. Example 8 of instant application recites specific dosages which are not in the claim; therefore Declarant's argument is not commensurate in scope with that claimed.

Also the declaration contains specific dosage amounts not recited in the claims. Ex parte Gelles 22 USPQ 2d 1318 (at 1319): "The evidence relied upon also should be reasonably commensurate in scope with the subject matter claimed and illustrate the claimed subject matter "as a class" relative to the prior art subject matter."

Also in order to claim unexpected result Applicant should note that there are three major points that should be considered:

The unexpected result must truly be unexpected, It must be commensurate in scope (show a trend representing the scope) and lastly a direct comparison with the closest prior art of record.

8. No claim is allowed

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL HARTLEY can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. V. G./
Examiner, Art Unit 1618,
07/27/10

/Robert C. Hayes/
Primary Examiner, Art Unit 1649